Tetrahedron Letters, Vol.29, No.3, pp 339-342, 1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

REMOTE FUNCTIONALIZATION ON THE STEROID β-FACE:** ATTACK ON CARBON-15

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Summary: 6β-(3'-Benzoylphenyl)acetoxy group is a good template for selective functionalization of carbon-15 of steroids.

Spectacular success in steroid remote functionalization utilized mainly templates attached to the hydroxyl group of 3α-cholestanol.[1] Steroid functionalizations by groups attached on the β-face were also recently described using benzophenone photochemical insertion[2] and chlorination via radical relay mechanism.[3] We wish to report here our recent results concerning a selective β-face functionalization which leads to 15-ketosteroids.

The steroid β-face is guarded by the C-18 and C-19 axial methyl groups which may hinder the approach of templates from the β-face. On the other hand, nmr chemical shift data on the methyl signals (18-H and 19-H) provide valuable information concerning the preferred conformations of the derivatives with aromatic templates on the β-face. For example, an upfield shift of the 18-H signal should indicate the approach of aromatic templates to the D-ring (and the side chain) region. Examination of a large number of 6β-steroidal derivatives[4] revealed that 6β-phenylacetamido group induced the largest upfield shift of the 18-H signal. Preference for a single methylene unit is obvious: it can be regarded as a bridge with the proper length and a minimum degree of freedom in reaching D-ring region. The amide linkage appears to be more ameanable to the desired conformation than the ester linkage due to its relative rigidity.

In the event, our first choice for possible remote functionalization was 3β-methoxy-6β-(3'-benzoylphenyl)acetamidocholestane (1),[5] which was synthesized from 3β-methoxy-6β-aminocholestane[6] and m-benzoylphenylacetic acid[7] in the presence of DCC in THF. When 1 (0.58 mM in degassed benzene) was irradiated 2.5 hours by medium pressure Hanovia lamp through uranium glass filter, two products were isolated in 24 % and 20 % yield from a complex product mixture.

**Dedicated to Professor A. I. Scott on the occasion of his 60th birthday.

The methyl singlet at δ 3.304 and the methylene singlet at δ 3.642 in the nmr spectrum of 1 were replaced by two sets of AB quartets in the nmr spectrum of each product indicating the activation of the methoxy methyl group and formation of diastereomeric 13-membered ring lactams 2. In this case, the presence of 3β-methoxy group provided an unexpected, yet favorable, target of hydrogen abstaction.

The next choice[8] was 6β-(3'-benzoylphenyl)acetoxy-3α,5α-cyclocholestane (3) easily prepared from i-cholesterol and m-benzoylphenylacetic acid in the presence of DCC and DMAP in pyridine. Irradiation of 3 (0.73 mM in degassed benzene) for 5.5 hours resulted in the formation of a mixture of mainly two unstable photoproducts, which was directly reduced by lithium aluminum hydride. Acetylation, dehydration by thionyl chloride, ruthenium (VIII) oxide cleavage,[9] and acid treatment afforded 15-ketocholesterol (4) in approximately 15 % unoptimized overall yield from 3. The initial photoproducts could thus be represented as the diastereomeric 12-membered ring lactones 5.

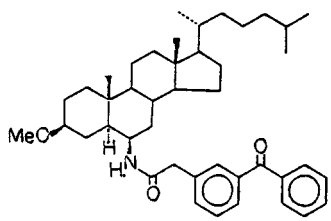
The selectivity achieved here reflects the ability of the starting material 3 to adopt the conformation like 6, in which the symmetry-allowed coplanar hydrogen abstraction [10] by $T_1(n,\pi^*)$ state of the benzophenone unit becomes favorable. In other words, the sigma bond of 15β-H can easily be made coplanar with the benzophenone carbonyl plane.

The usefulness of 6β-(3'-benzoylphenyl)acetoxy group for the activation of C-15 was further demonstrated with 3β-acetoxy-6β-(3'-benzoylphenyl)acetoxy-cholestane (7). When 7 (0.94 mM in degassed benzene) was similarly irradiated for 5 hours, a mixture of two diastereomeric products was formed in high yield, which was then transformed to 3β,6β-diacetoxy-15-ketocholesterol (8) in 42 % overall yield.

For activation of sites farther away, longer linkages are necessary in the templates. Incorporation of more methylene units renders the system too flexible and the selectivity suffers invariably.[11] For example, irradiation of 9 (0.78 mM in degassed benzene), m-benzoylbenzoate of i-cholesterol ethylene glycol ether, for 3.5 hours resulted in the formation of a complex product mixture, from which 16-ketocholesterol (10) was isolated in approximately 5 % yield after required transformations.

The photochemical behavior of another substrate 11 was studied briefly as an example with a longer, yet rigid, template, but there was no sign of any intramolecular photochemical reactions.[12]

The results show that selective β-face benzophenone photoinsertion can be achieved by the judicious choice of templates on the steroid molecule. Elaboration of template systems for selective functionalization of the side chain will be the subject of the future study.



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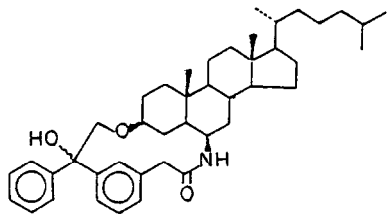

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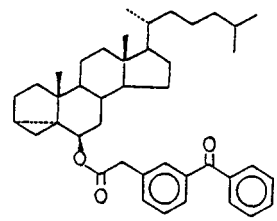

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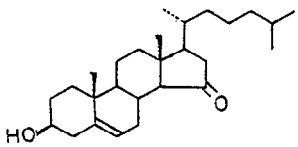

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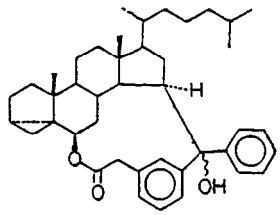

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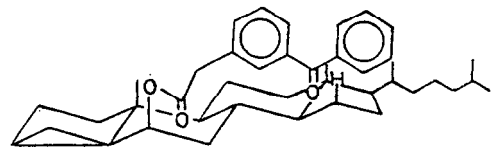

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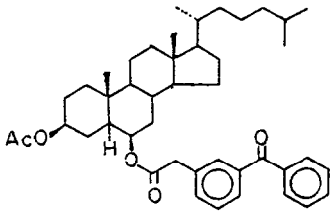

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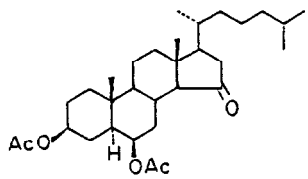

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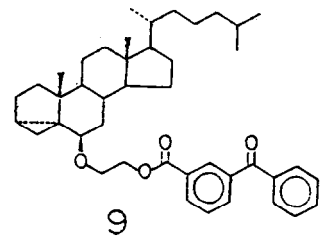

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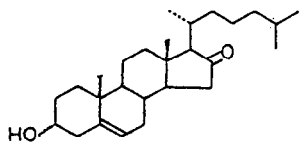

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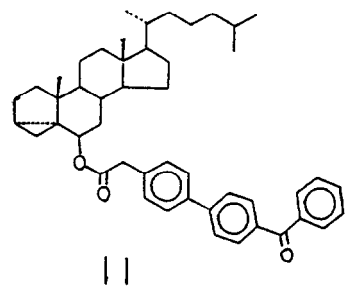

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ACKNOWLEDGEMENTS: This research was supported by a grant from Korea Science and Engineering Foundation. Authors wish to thank Dr. Y. Naya and Mr. H. Naoki of Suntory Institute for Bioorganic Research for obtaining nmr and ms data.

REFERENCES

1. a) For a most recent report, see R. Breslow and T. Guo, Tet. Lett., 1987, 28, 3187-3188.
b) For earlier works, see R. Breslow, Acc. Chem. Res., 1980, 13, 170-177.

2. R. Breslow, U. Maitra, and D. Heyer, Tet. Lett., 1984, 25, 1123-1126.

3. U. Maitra and R. Breslow, Tet. Lett., 1986, 27, 3087-3090.

4. Manuscript in preparation.

5. The structure of each substrate and product was determined unambiguously from complete physical data. See below for representative spectroscopic data for each compound.
1: nmr(360MHz, $CDCl_3$); δ5.480(1H,d,J=9.1Hz,N-H), 4.034(1H,m,6-H), 3.642(2H,s, benzylic), 3.304(3H,s,OCH_3), 3.106(1H,m,3-H), 0.882(3H,d,J=6.8Hz,21-H), 0.870&0.866(6H,d&d,J=6.5Hz,26-H&27-H), 0.565(3H,s,19-H), 0.493(3H,s,18-H): ms(EI); m/e 639(M^+,55%), 607(25), 416(22), 368(42), 240(62), 196(100), 105 (45).
2a(more polar lactam, 24% yield): nmr(360MHz, $CDCl_3$); δ5.103(1H,d,J=10.2Hz, N-H), 4.175&3.890(2H,d&d,J=11.0Hz,OCH_2), 4.090(1H,m,6-H), 3.780&3.428(2H, d&d,J=13.5Hz,benzylic), 3.423(1H,m,3-H), 0.882(3H,d,J=6.8Hz,21-H), 0.860& 0.855(6H,d&d,J=6.5Hz,26-H&27-H), 0.647&0.443(6H,s&s,18-H&19-H): ms(EI); m/e 639(M^+,53%), 609(90), 414(40), 368(29), 240(90), 223(75), 195(83), 105(100).
2b(less polar lactam, 20% yield): nmr(360MHz, $CDCl_3$); δ5.141(1H,d,J=11.0Hz, N-H), 4.450&3.939(2H,d&d,J=10.5Hz,OCH_2), 4.210(1H,m,6-H), 3.686&3.381(2H, d&d,J=14.0Hz,benzylic), 3.581(1H,m,3-H), 0.887(3H,d,J=6.5Hz,21-H), 0.862& 0.857(6H,d&d,J=6.7Hz,26-H&27-H), 0.653&0.334(6H,s&s,18-H&19-H): ms(EI); m/e 639(M^+,38%), 609(100), 414(40), 386(14), 240(48), 223(51), 195(62), 105(62).
4(as the acetate): nmr(300MHz, $CDCl_3$); δ5.383(1H,m,6-H), 4.592(1H,m,3-H), 2.030(3H,s,OAc), 1.013(3H,s,19-H), 0.996(3H,d,J=6.5Hz,21-H), 0.865&0.861(6H, d&d,J=6.5Hz,26-H&27-H), 0.764(3H,s,18-H): ms(CI); m/e 443(MH^+).
8: nmr(300MHz, $CDCl_3$): δ5.023(1H,m,6-H), 4.700(1H,m,3-H), 2.043&2.006(6H,s&s, OAc), 1.013(3H,s,19-H), 0.980(3H,d,J=6.5Hz,21-H), 0.856&0.852(6H,d&d,J=6.5 Hz,26-H&27-H), 0.773(3H,s,18-H): ms(SIMS); m/e 525(MNa^+).
10(as the acetate): nmr(300MHz, $CDCl_3$); δ5.380(1H,m,6-H), 4.612(1H,m,3-H), 2.036(3H,s,OAc), 1.050(3H,s,19-H), 0.970(3H,d,J=6.5Hz,21-H), 0.865&0.860(6H, d&d,J=6.5Hz,26-H&27-H), 0.835(3H,s,18-H): ms(CI); m/e 443(MH^+).

6. Prepared by LAH reduction of the oxime derivative of 3β-methoxy-6-ketocholestane.

7. Prepared from m-toluic acid following procedures adopted from J. A. Zderic, M. J. Kubitscheck, and W. A. Bonner, J. Org. Chem., 1961, 25, 1635-1637.

8. Unfortunately, we were unable to devise a viable method for the removal of the template portion from the lactams 2 and the use of the amide linkage was abandoned in the following studies.

9. The reaction protocol was adopted from professor Breslow's earlier reports. See the reference 2.

10. N. J. Turro, "Modern Molecular Photochemistry", The Benjamin/Cummings Publishing Co., Inc., Menlo Park, California, 1978, p.222.

11. Note also the less selective functionalizations reported in the reference 2.

12. The negative result was not unexpected. 4-Phenylbenzophenone gives mainly $T_1(\pi,\pi^*)$ state which is much less active in hydrogen abstraction compared to benzophenone $T_1(n,\pi^*)$ state. See N. J. Turro and C. G. Lee, Mol. Photochem., 1972, 4, 427-435.

(Received in Japan 19 October 1987)